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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,151	10/17/2003	Paul Ashton	CDSI-P01-020	8861

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EXAMINER	
NEGIN, RUSSELL SCOTT	
ART UNIT	**PAPER NUMBER**
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/688,151	ASHTON, PAUL	
	Examiner	Art Unit	
	Russell S. Negin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *18-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 30-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 7 June 2007 are acknowledged and the amendments are entered.

Accordingly, claims 1-34 are pending and claims 1-17 and 30-34 are examined on the merits in this Office action.

Specification

The objection to the disclosure because it contains an embedded hyperlink and/or other form of browser-executable code is withdrawn in view of amendments to the specification filed on 7 June 2007.

Claim Objections

The objection to claim 2 because of informalities is withdrawn in view of amendments made by applicant to the claim filed on 7 June 2007.

Priority

The application claims benefit to two provisional applications: 60/419,484 filed on 17 October 2002, and 60/468,964, filed on 7 May 2003. Please note that only claims 1-3 and 31 are granted a benefit date of 17 October 2002. The information disclosed concerning optical coherence tomography scanners (claims 4-5), corticosteroids

(claims 6-9), intraocular implants (claims 10-13), triamcinolone acetonides (claims 14-17), and toxicities (claims 32-34), are not disclosed in provisional application 60/419,484, and are granted the benefit date of 7 May 2003.

Claim Rejections - 35 USC § 101

The rejections of claims 1-17 and 30-34 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter are withdrawn in view of further consideration of the Office.

Claim Rejections - 35 USC § 102

The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Haybittle et al. [British Journal of Cancer, 1982, volume 45, pages 361-366] is withdrawn in view of amendments made by applicant to the claim filed on 7 June 2007.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

<u>The following rejections are reiterated from the Office action of 8 January 2007:</u>

<u>35 U.S.C. 103 Rejection #1</u>:

Claims 1-3 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haybittle et al. [British Journal of Cancer, 1982, volume 45, pages 361-366] in view of Augsburger et al. [British Journal of Opthalmology, 1989, volume 73, pages 911-917] in view of Smerhovsky et al. [Environmental Health Perspectives, January 2001, volume 109, pages 41-45].

Claim 1 is drawn to a method for monitoring the effectiveness of a regimen for treatment of an ocular disease comprising six steps:

--obtaining from a subject one or more measurements from self-reported data and other types of measurements;

--treating a subject with a regimen for a selected period of time;

--obtaining from a subject who has been treated one or more measurements;

--determining changes in the measurements induced by the regimen by comparing the first and third steps;

--comparing the measurements and/or changes in measurements to a signature, said signature representing probability relationships between one or more predictor variables and clinical outcomes of the disease;

--determining from the comparison in step (v) a probability that continued treatment of the subject with the regimen will result in a favorable clinical outcome;

wherein the identities of the predictor variables are determined by correlating previously-obtained clinical outcomes with previously obtained measurements selected from various types of measurements, and mathematical combinations thereof, said correlations being derived by using at least one automated non-linear algorithm.

Claim 2 is dependent from claim 1 with the additional limitation that the disease is an ocular disease, the clinical outcome is an increase in visual activity, and the measurement is a measure of retinal thickness.

Claim 3 is dependent from claim 2 with the additional limitation that the disease is a macular disease.

Claim 30 is dependent from claim 2 in which a method for treating an ocular disease, comprising administering a drug indicated for treatment of an ocular disease, and monitoring the effectiveness of said administration.

The article of Haybittle et al. studies a prognostic index in primary breast cancer, and states in the abstract:

> From a multiple-regression analysis of prognostic factors and survival in a series of 387 patients with primary breast cancer, a prognostic index has been constructed, based on lymph-node stage, tumour size and pathological grade. This index is more discriminating than lymph-node stage alone, and enables a larger group of patients to be identified with a very poor prognosis.

The study and step (i) of the method are taught under "Patients and Methods" on page 361 of Haybittle et al.:

> The patients for this study were taken from the first 500 consecutive female patients with primary operable invasive carcinoma of the breast seen and treated, under the care of a single surgeon, by simple mastectomy and triple-node biopsy at the Nottingham City Hospital. The prognostic factors selected for investigation were age, menopausal status,... tumour size measured in the fresh mastectomy specimen, lymph-node involvement judged by histology, tumour grade, cellular reaction, presence of sinus histiocytosis in lymph nodes, and oestrogen-receptor (RE) content of the primary.

Consequently, a plurality of measurements is taken from 500 subjects.

In step (ii), the treatment involved was either mastectomy (as explained above), and/or adjuvant chemotherapy, as explained in the first column of page 362 of Haybitttle et al.

Patient survival (i.e. step (iii)), is measured periodically (Figure 1 on page 363 of Haybittle et al.) throughout the five year following initiation of the study. Changes in survival (step (iv)) can be viewed by comparing the survival at 0 years to survival at any time throughout the first five years following commencement of the study.

Additionally, measurements of other parameters (i.e. size, lymph-node stage, and tumour grade) are obtained throughout the study and are used to form a prognostic index listed in the equation in the second column of page 363 of Haybittle et al. This prognostic index serves as a "signature" in the instant application (step (v)). This prognostic index (or "signature") is fit to the empirical data in Figure 1 of Haybittle et al. in Figure 2 of Haybittle et al. on page 364. Consequently, through use of a prognostic index, a subject can obtain information resulting in probability of a favorable outcome (i.e. survival) by comparison of statistical model to previously obtained empirical data.

The coefficients in the equation of page 363 were derived using Cox regression analysis (i.e. see caption to Table II of Haybittle et al. on page 363).

Haybittle et al. does not go into the detail behind the Cox regression analysis. Cox regression analysis is inherently a non-linear method.

The article of Zhou, entitled, "Understanding the Cox regression models with time-change covariates," is used to illustrate this inherent property by stating in the introduction:

> The Cox regression model is invariably difficult for students to grasp, partly because it is so different from the classical linear regression models....

Zhou continues to show how the regression model is non-linear through showing how the Cox model is a parametric exponential regression model (i.e. equation 1 on

page 153 of Zhou). Page 155 of Zhou illustrates an automated algorithm with which to execute the Cox regression method.

Haybittle et al. as evidenced by Zhou does not show the application of their statistical techniques to ocular and macular diseases.

The study of Augsburger et al., entitled, "Clinical parameters predictive of enlargement of melanocytic choroidal lesions," states in the summary:

> The authors followed up 197 melanotic choroidal lesions (62 categorized as benign naevi, 76 classified as suspicious naevi, 41 diagnosed as dormant melanomas, and 18 categorized as active melanomas) left untreated after their initial clinical documentation.

The parameters obtained from the study are described at the top of the first column of page 912 of Augsburger et al. At the bottom of the first column of page 912, use of the Cox regression model is used to determine a prognosis for the ocular disease stated:

> Cox proportional hazards modeling was used to assess the prognostic value of the recorded clinical parameters for prediction of subsequent lesion enlargement.

Figures 4 and 5 on page 915 of Augsburger et al. illustrate a comparison and correlation of theoretical and measured enlargements of choroidal lesions as a function of time after the initiation of the study.

Augsburger et al. ends their article by stating at the bottom of the first column of page 917:

> Meanwhile our table showing the incidence of lesion enlargement as a function of the presence or absence of the three prognostic parameters identified by our best Cox model (Table 3) may prove useful to clinicians. Using this table a clinician can estimate the likelihood that a patient's melanocytic choroidal lesion will enlarge during up to five year of follow-up. If the estimated likelihood of lesion enlargement is high and the clinician elects to observe the patient rather than advise treatment, he will probably want to arrange for closely spaced follow-up evaluations. If, on the other hand, the likelihood of lesion enlargement appears to be low, the clinician may be more confident in arranging for longer intervals between follow-up examinations.

While Haybittle et al. fulfills the requirements of the instant independent claim in showing a method for monitoring the effectiveness of a regimen for treatment of a disease, Haybittle et al. is not specific to eye disease as required in the instant dependent claims. Augsburger et al. is specific to eye disease, but evaluates eye disease progression statistics without applying a treatment. Both Haybittle et al. and Augsburger et al. use Cox regression analysis to evaluate the disease statistics.

The study of Smerhovsky et al., entitled, "Risk of cancer in an occupationally exposed cohort with increased level of chromosomal aberrations," uses Cox regression analysis to evaluate cancer severity in several parts of the body, including eyes and breasts (see Table 5 on page 43 of Smerhovsky et al. for a listing of the types of cancers analyzed in the study and the description of statistical methods in column 1 of page 43 of Smerhovsky et al.). The study shows that Cox regression analysis is a tool for evaluating diseases not limited by the specific part of the human body.

It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to modify the statistical analysis of breast cancer of Haybittle et al. by use of analogous statistical analysis for eye disease of Augsburger et al. by use of the Cox regression study of Smerhovsky et al. because while Haybittle et al. is specific to breast cancer, Augsburger et al. uses the same statistical techniques and methodology in the absence of a treatment regimen for the eyes, and Smerhovsky et al. shows the advantage of the applicability of this common technique (Cox regression) as effective in analyzing disease in both mentioned parts of the body (eyes and breasts). Consequently, it would be obvious to conduct the same study of Augsburger et al. with

an analogous treatment component as shown in Haybittle et al. for the eyes based on the teachings of the "universal" applicability of the statistical technique demonstrated in Smerhovsky et al.

Response to Arguments

Applicant's arguments filed 7 June 2007 have been fully considered but they are not persuasive.

Applicant's arguments regarding the Haybittle et al. and the first 35 U.S.C. 103 rejection are on pages 10-13 of the Remarks of 7 June 2007.

Applicant first argues on page 11 of the Remarks of 7 June 2007 that while the article of Haybittle et al. discusses breast cancer, the amended set of claims are specific to ocular diseases. This specific argument is the rationale behind eliminating the 35 U.S.C. 102(b) rejection and reiterating the 35 U.S.C. 103 rejection. It is obvious to combine the breast cancer study using Cox regression of Haybittle et al. in view of Augsburger et al. and Smerhovsky et al. to examine eye disease using the same mathematical principles of Cox regression.

Applicant continues by stating on page 11 of the Remarks 7 June 2007:

> In addition, continued treatment (step vi) of a subject in Haybittle to result in a favorable outcome is not a possibility, as mastectomy is a treatment/regiment that cannot be continued or discontinued. The Examiner contends that the treatment/regimen of step (ii) exists in Haybittle as the adjuvant chemotherapy administered in addition to the mastectomy and biopsy treatments. However, Haybittle later stipulated that investigation of the application of the prognostic index excludes those patients treated with adjuvant chemotherapy (Haybittle, p. 363).

This argument is not persuasive because Haybittle et al. did conduct a study using Cox analysis using Adjuvant therapy, and the results are posted in Table II on

page 363 of Haybittle et al. Although it is possible to use these results of Haybittle et al. in the prognostic equations of the article, the author of the article chose in favor of other parameters due to a more fundamental correlation. It is obvious to one of ordinary skill in the art to add the beta and Z parameters of adjuvant therapy, or any other parameter of Table II of Haybittle et al., to the prognosis equations to result in a longer, more complex (but improved), equation as there is still a correlation, albeit weak, between prognosis and adjuvant therapy. Furthermore, page 363 of Haybittle et al. nowhere states per se that patients were excluded from the correlations of the prognostic index with therapies; page 363 of Haybittle et al. merely uses the properties with the strongest degrees of correlations to optimize an estimate between cancer properties and prognoses.

Applicant continues to argue on pages 12 and 13 of the Remarks of 7 June 2007, that the studies of Augsburger et al. and Smerhovsky et al. do not compensate for the alleged deficiencies of Haybittle et al. reference. These arguments are not persuasive because, as discussed above, the Haybittle et al. reference is not deficient and there is sufficient motivation to combine Haybittle et al. with Augsburger et al, and Smerhovsky et al.

35 U.S.C. 103 Rejection #2:

Claims 4-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haybittle et al. in view of Augsburger et al. in view of Smerhovsky et al. as applied to

claims 1-3 and 30 above, and further in view of Konno et al. [RETINA, volume 21, pages 57-61, 2001].

Claims 4-5 depend from claims 2-3, respectively, with the limitation of incorporating optical coherence tomography scanners.

Haybittle et al. as in view of Augsburger et al. in view of Smerhovsky et al. as applied to claims 1-3 and 30 above do not teach use of optical coherence tomography scanners as a form of analysis and treatment.

The study of Konno et al., examines retinal thickness measurements with optical coherence tomography and the scanning retinal thickness analyzer, and states as its purpose, "To assess the reproducibility of retinal thickness measurements in normal subjects and to compare foveal thickness using optical coherence tomography (OCT) and the scanning retinal thickness analyzer (RTA)."

Konno et al. elaborate in the last sentence of their article:

> We believe that both instruments might significantly contribute to early, accurate diagnosis and better monitoring of treatment of macular diseases, especially macular edema.

It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to modify Haybittle et al. in view of Augsburger et al. in view of Smerhovsky et al. as applied to claims 1-3 and 30 above, by use of Konno et al. because Konno et al. has the advantage of using OCT as a tool for diagnosis and treatment of the eye diseases (i.e. those modeled in Augsburger et al.) by comparing retinal thicknesses in patients to those of normal subjects (i.e. the subjects used in Konno et al.).

Response to Arguments

Applicant's arguments filed 7 June 2007 have been fully considered but they are not persuasive.

Applicant argues on pages 13 and 14 of the Remarks of 7 June 2007, that the studies of Augsburger et al., Smerhovsky et al. and Konno do not compensate for the alleged deficiencies of Haybittle et al. reference. These arguments are not persuasive because, as discussed above, the Haybittle et al. reference is not deficient.

35 U.S.C. 103 Rejection #3:

Claims 6-7, 10-11, and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haybittle et al. in view of Augsburger et al. in view of Smerhovsky et al. as applied to claims 1-3 and 30 above, in further view of Guo et al. [US Patent 6,217,895].

Claims 6-7 depend from claims 2-3, respectively, with the additional limitation of the usage of costicosteroids.

Claims 10-11 depend from claims 6-7, respectively, with the additional limitation of the usage of intraocular implants.

Claims 14-15 depend from claims 10-11, respectively, with the additional limitation of the usage of triamcinolone acetonide.

Haybittle et al. in view of Augsburger et al. in view of Smerhovsky et al. as applied to claims 1-3 and 30 above do not teach usage of corticosteroids, intraocular implants, or triamcinolone (or fluocinolone) acetonide in addressing eye diseases.

The patent of Guo et al., entitled, "Method for treating and/or preventing retinal diseases with sustained release corticosteroids," states in the abstract:

> The present invention relates to a method for administering a corticosteroid to a posterior segment of an eye. In the method, a sustained release device is implanted to implant the corticosteroid to the eye. The aqueous corticosteroid concentration remains less than vitreous corticosteroid concentration during release of corticosteroid from the device.

Lines 18-19 of column 2 of Guo et al. state the caption of Figure 1:

> Figure 1 shows the sustained release profile of a 2 mg fluocinolone acetonide implant in buffer.

Claim 18 of the reference also lists triamcinolone as a potential species to be substituted with fluocinolone.

It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to modify Haybittle et al. in view of Augsburger et al. in view of Smerhovsky et al. as applied to claims 1-3 and 30 above, in further view of the sustained release of acetonides in implants of Guo et al. because Guo et al. teach the required acetonide releasing implant for treatment of the ocular disorders capable of use in statistical analysis methodology taught in Augsburger et al., Haybittle et al., and Smerhovsky et al.

Response to Arguments

There are no arguments regarding this 35 U.S.C. 103 Rejection in the Remarks of applicant which were submitted on 7 June 2007.

35 U.S.C. 103 Rejection #4:

Claims 8-9, 12-13, and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haybittle et al. as evidenced by Zhou in view of Augsburger et al. in view of Smerhovsky et al. in view of Konno et al. as applied to claims 4-5 above, in further view of Guo et al. [US Patent 6,217,895].

Claims 8-9 depend from claims 4-5, respectively, with the additional limitation of usage of costicosteroids.

Claims 12-13 depend from claims 8-9, respectively, with the additional limitation of usage of intraocular implants.

Claims 16-17 depend from claims 12-13, respectively, with the additional limitation of usage of triamcinolone acetonide.

Haybittle et al. in view of Augsburger et al. in view of Smerhovsky et al. in view of Konno et al. as applied to claims 4-5 above do not teach usage of corticosteroids, intraocular implants, or triamcinolone (or fluocinolone) acetonide in addressing eye diseases.

The patent of Guo et al. studies a method for treating and/or preventing retinal diseases with sustained release corticosteroids, and states in the abstract:

> The present invention relates to a method for administering a corticosteroid to a posterior segment of an eye. In the method, a sustained release device is implanted to implant the corticosteroid to the eye. The aqueous corticosteroid concentration remains less than vitreous corticosteroid concentration during release of corticosteroid from the device.

Lines 18-19 of column 2 of Guo et al. state the caption of Figure 1:

> Figure 1 shows the sustained release profile of a 2 mg fluocinolone acetonide implant in buffer.

Claim 18 of the reference also lists tiamcinolone as a potential species to be substituted with fluocinolone.

It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to modify Haybittle et al. in view of Augsburger et al. in view of Smerhovsky et al. in view of Konno et al. as applied to claims 4-5 above, in further view of the sustained release of acetonides in implants of Guo et al. because Guo et al. teach the required acetonide releasing implant for treatment of the ocular disorders capable of use in statistical analysis methodology taught in Augsburger et al., Haybittle et al., and Smerhovsky et al.

Response to Arguments

Applicant's arguments filed 7 June 2007 have been fully considered but they are not persuasive.

Applicant argues on pages 14 and 15 of the Remarks of 7 June 2007, that the studies of Augsburger et al., Smerhovsky et al., Konno, and Guo et al. do not compensate for the alleged deficiencies of Haybittle et al. reference. These arguments are not persuasive because, as discussed above, the Haybittle et al. reference is not deficient.

35 U.S.C. 103 Rejection #5:

Claims 31-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haybittle et al. in view of Ando et al. [US PGPUB 2004/0039620, published on 26 February 2004, filed 21 September 2001].

Claims 31 is drawn to a method for conducting a drug discovery business comprising six steps:

--obtaining measurements selected from a group of possible measurements;

--treating the test animal with a test compound for a selected period of time;

--obtaining one or more measurements following treatment;

--determining changes in the measurements induced by the regimen;

--comparing the measurements or changes in measurements to a signature;

--determining from the comparison data, the suitability of further clinical treatment;

wherein the identities of the predictor variables are determined by correlating pre-determined physiological states, or responses to known drugs with previously obtained measurements; said correlations being derived by using a non-linear algorithm.

Claim 32 is dependent from claim 31 with the additional limitation of conducting therapeutic profiling of a test compound determined to be suitable for further clinical development.

Claim 33 is dependent from claim 31 with the additional limitation of preparing a structural analogue of a test compound determined to be suitable for further clinical development and conducting therapeutic profiling of said analogue for efficacy and toxicity in animals.

Claim 34 is dependent from claim 32 or claim 33 further comprising licensing a test compound determined to be suitable for further clinical development, or an analogue thereof, to another business for clinical trials in human subjects.

The article of Haybittle et al. studies a prognostic index in primary breast cancer, and states in the abstract:

> From a multiple-regression analysis of prognostic factors and survival in a series of 387 patients with primary breast cancer, a prognostic index has been constructed, based on lymph-node stage, tumour size and pathological grade. This index is more discriminating than lymph-node stage alone, and enables a larger group of patients to be identified with a very poor prognosis.

The study and step (i) of the method are taught under "Patients and Methods" on page 361 of Haybittle et al.:

> The patients for this study were taken from the first 500 consecutive female patients with primary operable invasive carcinoma of the breast seen and treated, under the care of a single surgeon, by simple mastectomy and triple-node biopsy at the Nottingham City Hospital. The prognostic factors selected for investigation were age, menopausal status,... tumour size measured in the fresh mastectomy specimen, lymph-node involvement judged by histology, tumour grade, cellular reaction, presence of sinus histiocytosis in lymph nodes, and oestrogen-receptor (RE) content of the primary.

Consequently, a plurality of measurements is taken from 500 subjects.

In step (ii), the treatment involved was either mastectomy (as explained above), and/or adjuvant chemotherapy, as explained in the first column of page 362 of Haybitttle et al.

Patient survival (i.e. step (iii)), is measured periodically (Figure 1 on page 363 of Haybittle et al.) throughout the five year following initiation of the study. Changes in survival (step (iv)) can be viewed by comparing the survival at 0 years to survival at any time throughout the first five years following commencement of the study.

Additionally, measurements of other parameters (i.e. size, lymph-node stage, and tumour grade) are obtained throughout the study and are used to form a prognostic

index listed in the equation in the second column of page 363 of Haybittle et al. This prognostic index serves as a "signature" in the instant application (step (v)). This prognostic index (or "signature") is fit to the empirical data in Figure 1 of Haybittle et al. in Figure 2 of Haybittle et al. on page 364. Consequently, through use of a prognostic index, a subject can obtain information resulting in probability of a favorable outcome (i.e. survival) by comparison of statistical model to previously obtained empirical data.

The coefficients in the equation of page 363 were derived using Cox regression analysis (i.e. see caption to Table II of Haybittle et al. on page 363).

Haybittle et al. does not go into the detail behind the Cox regression analysis. Cox regression analysis is inherently a non-linear method.

The article of Zhou, entitled, "Understanding the Cox regression models with time-change covariates," is used to illustrate this inherent property by stating in the introduction:

> The Cox regression model is invariably difficult for students to grasp, partly because it is so different from the classical linear regression models....

Zhou continues to show how the regression model is non-linear through showing how the Cox model is a parametric exponential regression model (i.e. equation 1 on page 153 of Zhou). Page 155 of Zhou illustrates an automated algorithm with which to execute the Cox regression method.

Haybittle et al. as evidenced by Zhou do not teach the clinical development, drug determination, and licensing.

The application of Ando et al. studies a system for evaluating profitability of developed medicine, and discloses in the abstract,

> A profitability-evaluating system for a medical drug candidate under development comprises a data set-creating subsystem and a management index-creating subsystem.... With the above arrangement, there is provided the system for evaluating a profitability from an investment in the research and development of a medical drug, by utilizing the real option method.

Paragraph [0052] of Ando et al. elaborates on the best mode for clinical development:

> Hereinafter, preferred embodiments of the present invention will be described with reference to the accompanying drawings. In the profitability-evaluating system of the present invention, the developing term from development of a medical drug to the time when the sale of the medical drug is started is divided into a plurality of developing stages, and an evaluation point is set at each time of judging whether or not the development is advanced to the next developing stage, and a profitability of the next developing stage is evaluated at the evaluation point. It is also possible to add a basic researching stage prior to the clinical development, to this developing term and divide this total term into a plurality of developing stages.

Paragraph [0135] of Ando et al. elaborates on licensing for other companies:

> In addition to the above expenses, other relevant expenses may be included in the operation parameters, if needed. For example, outcome study cost, royalties paid for the license to use the patents of other companies, etc. are included therein. The fluctuation of royalties can be supposed in accordance with, for example, the pattern of a normal distribution.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the statistical method of disease analysis of Haybittle et al. by use of the drug development business method of Ando et al., because Ando et al. has the advantage of proposing a protocol for a business method to which drugs (such as the medicines proposed in the other prior art references) can be applied in a safe and profitable manner.

Response to Arguments

Applicant's arguments filed 7 June 2007 have been fully considered but they are not persuasive.

Applicant has two arguments regarding this 35 U.S.C. 103 Rejection.

Applicant first argues on pages 15-17 of the Remarks of 7 June 2007, that the Ando et al. reference does not compensate for the alleged deficiencies of the Haybittle et al. reference. These arguments are not persuasive because, as discussed above, the Haybittle et al. reference is not deficient in the aspects recited by applicant.

Additionally, applicant asserts that there is no motivation to combine Ando et al. and Haybittle et al. The motivation is stated preceding these arguments. Even assuming, en arguendo, that this motivation is deficient, when taking into account the recent Supreme Court decision of KSR International v. Teleflex, there is additional rationale to combine these references in that:

> Known work in one field of endeavor may prompt variations of it for use in either the same field of a different one based on design incentives or other market forces...

In this instance, modifying the study of Haybittle et al. to make it market accessible yields predictable results (i.e. profits). In other words, by making the prognosis index of Haybittle et al. profitable, one is adjusting an academic study to make it function under market conditions leading to accumulation of the design incentive- income.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Ram Shukla, Supervisory Patent Examiner, can be reached at (571) 272-0735.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

8/16/07

RSN
16 August 2007

/Shubo (Joe) Zhou/

SHUBO (JOE) ZHOU, PH.D.
PRIMARY EXAMINER